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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,427	11/14/2001	David Botstein	P2730P1C10	4110

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EXAMINER	
MURPHY, JOSEPH F	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,427	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Joseph F. Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-123* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Claims 119-123 are pending and under consideration.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/13/2005 has been entered.

The Declaration under 37 CFR 1.132 filed 9/13/2005 is insufficient to overcome the rejection of claims 119-123 based upon 35 USC 101, 112 first paragraph as set forth in the last Office action for the reasons set forth below.

Claim Rejections - 35 USC §§ 101, 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 119-123 are rejected under 35 U.S.C. § 101 because they are drawn to an invention with no apparent or disclosed patentable utility, for reasons of record set forth in the Office Action of 4/19/2004, 11/1/2004 and 6/13/2005. The instant application has provided a description of an isolated DNA encoding a protein, the protein encoded thereby and antibodies to

the protein. The instant application does not disclose the biological role of this protein or its significance. Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

The data in the Specification show that gene expression is increased in tumor cell lines and primary tumors. No data is presented regarding the levels of protein expression. It does not necessarily follow that a decrease in copy number of the mRNA results in a change in protein expression that would correlate to the disease state, and thus it does not follow that an antibody to the polypeptide would correlate to the disease state. Haynes et al. (Electrophoresis 19:1862-1871, 1998) studied 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein sand transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. Haynes concluded that the protein levels couldn't be accurately predicted from the level of the corresponding mRNA transcript (page 1863, second paragraph and Figure 1).

The Specification additionally sets forth that the PRO830 is homologous to known proteins. However, it is commonly known in the art that sequence-to-function methods of assigning protein function are prone to errors (Doerks et al.1998). These errors can be due to sequence similarity of the query region to a region of the alleged similar protein that is not the active site, as well as homologs that did not have the same catalytic activity because active site residues of the characterized family were not conserved (Doerks et al. page 248, column 3, fourth and fifth paragraphs). Inaccurate use of sequence-to-function methods have led to significant function-annotation errors in the sequence databases (Doerks et al. page 250, column 1, third paragraph). Furthermore, Brenner (1999, Trends in Genetics 15:132-133) argues that

accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

After complete characterization, the protein may be found to have a patentable utility, and thus an antibody that binds this protein would have a patentable utility. This further characterization, however, is part of the act of invention and until it has been undertaken Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson,* 148 USPQ 689 (Sup. Ct., 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 USC § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to

engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

The instant claims are drawn to an antibody that binds a polypeptide which has an as yet undetermined function or biological significance. Until some actual and specific significance can be attributed to the protein identified in the specification as PRO830, the instant invention is incomplete. The polypeptide encoded by the nucleic acids of the instant invention is alleged to be structurally analogous to proteins that are known in the art as, *inter alia*, HSU88154. In the absence of knowledge of the natural substrate or biological significance of this protein, there is no immediately obvious patentable use for it. To employ an antibody that binds a protein of the instant invention in the identification of substances that inhibit the proteins activity is clearly to use it as the object of further research that has been determined by the courts to be a non-patentable utility. Since the instant specification does not disclose a "real world" use for PRO830 then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 USC § 101 as being useful.

Applicant presents the 1.132 Declaration by Goddard, and argues that the utility for the antibodies to the PRO830 polypeptides is based on a 2.188 to 2.549-fold gene amplification observed for the DNA encoding PRO 830 in lung tumors, and that the data was presented in Example 170 on page 539 of the Specification. Appellant quotes from p. 3 of the declaration as giving an expert opinion that a 2-fold increase in gene copy number in a tumor sample relative to a non-tumor sample is significant and useful. Appellant concludes that one skilled in the art would consider the 2.173 to 2.514-fold amplification of the gene encoding PRO830 in three lung tumors is significant and credible based upon the facts in the Goddard declaration. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert

testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2.173 to 2.514-fold amplification of the gene encoding PRO830 in three lung tumors is significant and credible. Credibility has never been questioned. However, the significance can be questioned since eleven of the fourteen lung tumor samples did not show an amplification of the gene encoding PRO830, and the control used was not a matched non-tumor lung sample but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al., Konopka et al.). Hu et al. and Chen et al. speak to the strength of the opposing evidence, as do Pennica et al., Konopka et al., Haynes et al., Gygi et al., Lian et al., and Fessler et al., discussed in the rejection above. The expert has interest in the outcome of the case since Dr. Goddard is listed as an inventor and is employed by the assignee. Finally, the expert refers to three publications as factual support for the conclusions in the declaration. However, neither Livak et al. nor Heid et al. appear to indicate that an approximately 2-fold amplification of genomic DNA is significant in tumors. Pennica et al. was found to support the rejection, as discussed in the rejection above. The Goddard declaration evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO830 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such.

Similarly, the PRO830 gene has *not* been shown to be useful to track the efficacy of cancer therapy. The specification merely demonstrates that the PRO830 genomic DNA may be amplified in some cancers, to a minor degree (about 2.5 fold) compared to normal DNA from blood. No mutation or translocation of PRO830 has been associated with any type of cancer versus normal tissue. It is not known whether PRO830 is amplified in corresponding normal tissues, and what the relative levels of amplification are. In addition, there is no correlations shown between the increase in gene amplification and amplification f the target protein. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO830 may be amplified in a variety of samples and invites the artisan to determine the significance of this increase. It remains that, as evidenced by Pennica et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment.

Applicant argues that the Haynes et al. publication does not support the rejection. Applicant characterizes Haynes et al. as teaching that there is a general trend but no strong correlation between protein expression level and transcript level. Applicant criticizes Haynes et al. for being directed to a study of yeast proteins. Applicant further characterizes Haynes et al.'s conclusions as showing that there is a positive correlation between transcript and protein for most of the 80 yeast proteins studied, but the correlation is not linear and thus one cannot accurately predict protein levels from mRNA levels. Applicant stresses that very few data points scattered away from the expected normal or showed a lack of correlation between mRNA and protein. Applicant concludes that Haynes et al. show that it is more likely than not that a positive correlation exists between mRNA and protein levels. This has been fully considered but is not found to be persuasive. In the instant case, the specification provides data showing a very small

increase in DNA copy number, approximately 2-fold, in a few tumor samples for PRO830. There is no evidence regarding whether or not the PRO830 mRNA or protein levels are also increased in these tumor samples. Since the instant claims are directed to PRO830 protein, it was imperative to find evidence in the relevant scientific literature whether or not a small increase in DNA copy number would be considered by the skilled artisan to be predictive of increased in mRNA and protein levels. Haynes et al. was cited as providing evidence that protein levels cannot be accurately predicted from mRNA levels, and that variances as much as 40-fold or even 50-fold were not uncommon (p. 1863). Haynes et al. used yeast as an art-accepted model for eukaryotic systems. Given how small the DNA copy number of PRO830 increased, and the evidence provided by Haynes et al., Pennica et al. and Konopka et al., it was clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or protein levels. One skilled in the art would do further research to determine whether or not the PRO830 protein levels increased significantly in the tumor samples. Such further research requirements makes it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in Brenner v. Manson, 148 U.S.P.Q. 689, cited above.

Applicant refers to three additional articles (Orntoft et al., Hyman et al. and Pollack et al.) as providing evidence that gene amplification generally results in elevated levels of the encoded protein. Applicant characterizes Orntoft et al. as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in

mRNA transcripts. Applicant characterizes Hyman et al. as providing evidence of a prominent global influence of copy number changes on gene expression levels. Applicant characterizes Pollack et al. as teaching that 62% of highly amplified genes show moderately or highly elevated expression and that, on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA levels. This has been fully considered but is not found to be persuasive. Ornitoft et al. appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and protein levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Ornitoft et al. do not appear to look at gene amplification, mRNA levels and protein levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Ornitoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO830 in the instant specification. That is, it is not clear whether or not PRO830 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance of Ornitoft et al. is not clear. Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Protein levels were not investigated. Therefore, Hyman et al. also do not support utility of the claimed proteins. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate protein levels. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention. Importantly, none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research

was relevant to the development of potential cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the claimed PRO830 proteins have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

Applicant presents a declaration by Dr. Polakis filed with the response under 37 CFR 1.132. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen proteins have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in protein levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. First, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO830 in tumor samples relevant to normal samples. Only gene amplification data was presented. In addition, Applicant argues that the Polakis Declaration demonstrates that the preponderance of the evidence suggests that there is a correlation between protein levels and mRNA levels. The data presented in the Polakis declaration found that out of 200 gene transcripts that are present in human tumors, only ca. 12% had a correlation between increases in the level of mRNA transcripts and protein expression.

Therefore, the declaration is insufficient to overcome the rejection of claims 119-123 based upon 35 U.S.C. §§ 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and protein levels, and not gene amplification levels and protein levels. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a micoarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). In addition, Hancock states "the markers that are generated by proteomics are not always consistent with the markers that are generated from expression profiling".

Applicant further submits a Declaration filed pursuant to 37 CFR 1.132 by Dr. Ashkenazi. In the Declaration Dr. Ashkenazi states that even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product,

this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment, because if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. The Declaration of Dr. Ashkenazi further states that the absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

However, the assertion that a difference in gene expression compared to gene amplification enables more accurate tumor classification is a conclusory statement. No evidence is provided of a tumor where this difference has aided classification, and there is further no evidence of a tumor wherein a difference in expression relative to amplification aided a clinician in ruling out potential treatment agents. Indeed, the art shows that further experimentation is necessary to determine a use for the gene of interest. Wang et al. teaches that differential display is the first of many steps required in the discovery of a novel pharmacological target, especially given that the function of the factor is most likely unknown. Therefore, further action should be taken to characterize the functions of a particular gene of interest, including ... validation for the importance of the gene in disease processes. See Wang, page 279, column 2, full paragraph 1.

For all of these reasons, the rejections are maintained.

Claims 119-123 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well

established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

Claims 119-123 are rejected.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Murphy whose telephone number is (571) 272-0877. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (571) 272-0829.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Joseph F. Murphy, Ph. D.
Primary Examiner
Art Unit 1646
November 22, 2005

JOSEPH MURPHY
PATENT EXAMINER